by TLR activation is a double-edged sword, defending against infection but also potentially harmful to the host, because aberrant activation may lead to autoimmunity and inflammatory disease. Within the framework of this understanding, it is hoped that future studies will permit the development of targeted therapies for both infectious and autoimmune diseases.

Further reading

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Learning to reach for ‘invisible’ visual input

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Patients who have suffered damage to primary visual cortex can report being blind but display some proficiency when manually interacting with ‘unseen’ objects — a phenomenon known as blindsight [1–4]. There is conflicting evidence about analogous situations in normally sighted people [5–7]; however, to date no study has attempted to assess a *directly* analogous situation, to have normally sighted people *interact* with unseen stimuli. We used a form of binocular masking to suppress awareness of oriented stimuli [8]. Despite initial insensitivity when making verbal judgements, participants who reached as if to grasp perceptually suppressed stimuli displayed increasing proficiency with training and feedback. This was not simply due to practise, as another group did not develop such proficiency when completing a matched number of trials, with feedback, while making verbal responses; however, this same group subsequently developed sensitivity when they too completed training with reaching and feedback. Our data thus reveal a special status for attempts to grasp perceptually suppressed stimuli.

We used presentations of high contrast white noise to one eye to suppress awareness of pairs of oriented lines in the other eye (Figure 1 and see Supplemental

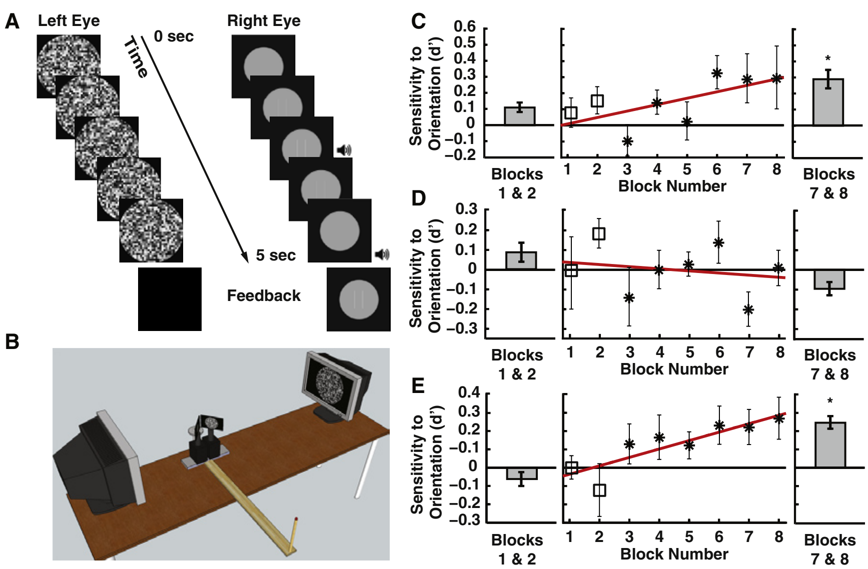

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Figure 1. Example trial sequence, experimental apparatus and data from Experiments 1–3.
(A) Depiction of a trial sequence with a vertical target stimulus. Target stimuli reached peak contrast 2.5 seconds into the trial, accompanied by a tonal pip to prompt the participant to respond. A second pip signalled the conclusion of the trial and, on reaching trials, let participants know they could return their hand to a resting position. When feedback was provided, it was presented for one second following the five second trial sequence (Supplemental Movie 1). (B) Depiction of experimental apparatus from the right rear. Participants sat with their head on a chinrest and observed the stimulus presentation via half silvered mirrors. (see Supplemental Information for further details). (C) Participant sensitivity (d') to the target orientation in eight blocks of trials from Experiment 1. In the first two blocks of trials, given by the box data points in the central panel, participants responded verbally and were given no feedback. In the final six blocks of trials (star data points), participants responded by reaching out and pretending to grasp the oriented target and were given trial-by-trial feedback. The red line shows a linear regression to the data. Bar plots show participants’ overall performance during the first (left panel) and last (right panel) two blocks of trials. In these plots a star indicates that this level of sensitivity was significantly different from zero. Error bars show ± 1 SEM. (D) and (E) show the same as (C) for Experiments 2 and 3, respectively.

Information published with this article online). Suppressed lines were vertical or horizontal, presented in a pseudo-random order. Participants completed eight blocks of 100 trials. In the first two blocks participants attempted to identify stimulus orientation verbally, and no feedback was provided. Performance scores were converted into measures of sensitivity (*d'*), as per signal detection theory. Analysis revealed that participants were insensitive to 'unseen' stimulus orientation during these initial blocks of trials ($d' = 0.11$, SEM = 0.06; $t_9 = 1.85$, $p = 0.1$, one sample; Figure 1C).

Having established a baseline of insensitivity, participants completed six additional blocks of trials wherein they would reach, as if to grasp 'unseen' stimuli, while we recorded the orientation of their hand (see Supplemental Information for further details). During these blocks, trial-by-trial feedback was provided concerning task performance and participants could see their hand. Note, however, that task performance relied on the same visual information as in preceding verbal trials, as 'unseen' stimuli were simulated, not physical. There was thus no additional proprioceptive information. We found that performance steadily improved with practise (linear regression; $F_{1,39} = 4.59$, $p = 0.039$; Figure 1C), such that by the final two blocks performance had risen above chance ($d' = 0.29$, SEM = 0.12; $t_9 = 2.46$, $p = 0.03$; Figure 1C), despite participants insisting they could not *see* the oriented lines (see Supplemental Information, Experiment 5, for matching data from trials with auditory feedback).

As performance had steadily improved, it was possible that this was due to practise *per se*, rather than attempts to grasp unseen stimuli. We therefore recruited a second group of participants who completed a matched number of trials while providing verbal reports. In the first two blocks of trials no feedback was provided. Again, participants were insensitive to perceptually suppressed stimulus orientation ($d' = 0.09$, SEM = 0.09; $t_9 = 0.87$, $p = 0.41$; Figure 1D). These participants then completed six additional blocks of trials, providing verbal reports and receiving trial-by-trial feedback as to task performance. This did not result in a steady improvement in sensitivity ($F_{1,39} = 0.36$, $p = 0.55$; Figure 1D), so participants remained insensitive to perceptually suppressed stimulus orientation in the final two blocks of trials ($d' = -0.09$, SEM = 0.07; $t_9 = 1.4$, $p = 0.195$; Figure 1D).

Our first group of participants had attempted to reach as if to grasp 'unseen' stimuli and showed improved sensitivity with practise and feedback. Our second group made verbal reports and showed no such improvement. It was possible that this dissociation was due to the insensitivity of the second group, as opposed to the response mode during training. We therefore tried to replicate Experiment 1 using this second group of participants. The initial two blocks of trials, involving verbal reports without feedback, confirmed continued insensitivity to perceptually suppressed stimulus orientation ($d' = -0.06$, SEM = 0.08; $t_9 = 0.81$, $p = 0.44$; Figure 1E). Participants then completed six blocks of reaching trials with feedback, and sensitivity improved ($F_{1,39} = 8.61$, $p = 0.006$; Figure 1E), resulting in statistically significant sensitivity in the final two blocks of trials ($d' = 0.24$, SEM = 0.07; $t_9 = 3.44$, $p = 0.007$; Figure 1E).

In experiments described thus far, we made no attempt to record how confident participants felt when making judgments about 'unseen' stimuli. We therefore completed a final experiment wherein participants reached as if to grasp perceptually suppressed stimuli while we recorded the orientation of their hand, and then recorded not only if they felt they had seen the stimulus, but also if they felt confident they had grasped for the appropriate orientation. Of 3000 trials completed by five participants, there was only 1 trial in which visibility was reported. There was, however, a robust correlation between task performance and confidence ($r = 0.65$, $p < 0.01$). This is consistent with some reports of clinical blindsight [9], and with an attempt to induce an analogous situation in normally sighted people using transcranial magnetic stimulation [7].

It is thought that blindsight is possible as two visual systems exist; one that facilitates conscious visual awareness, which is damaged in cortically blind people, and another that mediates vision for action [4,10]. If improved sensitivity from training to reach for 'unseen' stimuli results from vision for action, it should only occur when reaching for contemporary signals [10]. We therefore used trained participants to reach for contemporary signals, or for signals that had been presented a short time ago. Sensitivity was observed for the former ($d' = 0.27$, SEM = 0.04; $t_4 = 6.45$, $p = 0.003$, one sample) but not the latter ($d' = -0.05$, SEM = 0.04; $t_4 = -1.18$, $p = 0.3$, one sample; Supplemental Information, Experiment 6) type of trial.

Our data establish a special status for attempts to *grasp* 'unseen' stimuli relative to verbal reports. Practise with feedback when attempting to grasp unseen stimuli resulted in a modest level of sensitivity after a relatively brief training period, but this did not happen for attempts at verbal description. While it is possible this difference would diminish with extended training, our data clearly indicate an advantage in training efficacy for attempts to grasp unseen stimuli. This may be relevant for developing training protocols for cortically blind patients.

Supplemental Information

Supplemental Information includes two figures, one movie, Supplemental Results and Supplemental Experimental Procedures, and can be found with this article online at doi:10.1016/j.cub.2011.05.036.

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